REMARKS

Claims 1, 7-21 and 29-50 are pending. Claims 34-50 are withdrawn as being directed to a non-elected invention. Claims 1, 7-21, and 29-33 are rejected under 35 U.S.C. § 103(a) for obviousness over WO 99/01034 in view of WO 00/69449, WO 01/74164, Kishimoto et al. (Genes Dev. 14:1181-1185, 2000; hereinafter "Kishimoto"), and Zhu et al. (Cancer Res. 64:7918-7926, 2004; hereinafter "Zhu"). By this reply, Applicants address each of the Office's rejections.

Telephone Interview with Examiner Gough and Examiner Weber

Applicants wish to thank Examiners Gough and Weber for the courtesy of a telephonic interview on June 5, 2008. Examiner Weber acknowledged that WO 99/01034 and WO 00/69449 should be withdrawn from the present obviousness rejection because they add nothing beyond WO 01/74164. Accordingly, only the combination of WO 01/74164 and Kishimoto with Zhu need be discussed in response to the present rejection of claims 1, 7-21, and 29-33. For the reasons discussed below, WO 01/74164, Kishimoto, and Zhu, either singly or in combination, fail to teach or suggest all of the limitations of present claims 1, 7-21, and 29-33. Applicants respectfully request reconsideration of the rejection of these claims under 35 U.S.C. § 103(a). Applicants further request that the Office contact the undersigned by telephone in order to resolve any remaining issues in this case.

Rejections under 35 U.S.C. § 103(a)

Claims 1, 7-21, and 29-33 stand rejected under 35 U.S.C. § 103(a) for obviousness over the combination of WO 99/01034, WO 00/69449, WO 01/74164, Kishimoto, and Zhu. As is discussed above, the Office acknowledged during the telephonic interview of June 5, 2008 (the "Interview") that WO 99/01034 and WO 00/69449 should be withdrawn from the rejection. Thus, Applicants only address the rejection of claims 1, 7-21, and 29-33 based on the combination of WO 01/74164, Kishimoto, and Zhu.

Independent claim 1 and claims dependent therefrom are directed to a method for cultivating hair inductive cells, such as dermal papilla (DP) cells and dermal sheath (DS) cells, by culturing these cells in a culture medium that includes a medium conditioned by prostate epithelial cells. The Office states that WO 01/74164 "teaches a method comprising culturing dermal papilla (DP) cells with cells expressing Wnt proteins to promote hair growth" (Office Action, p. 4), while Kishimoto "show[s] that the hair inductive activity of DP cells is maintained in culture by Wnt signaling and that exogenous Wnt would extent [sic] hair cycle and promote hair growth" (Office Action, p. 5). The Office states that "[w]hile [WO 01/74164 and Kishimoto] do not teach prostate epithelial cells specifically, these cells are known the [sic] express Wnt, as is evidenced by Zhu who show expression of nearly all 19 Wnt genes" (Office Action, p. 5; emphasis added). The Office concludes by stating that given the combined disclosures of WO 01/74164, Kishimoto, and Zhu, it would have been obvious to one of ordinary skill in the art to cultivate hair inductive cells such as dermal papilla (DP) cells in a medium that includes medium conditioned by prostate epithelial cells, that one of skill in the art

would be motivated to do so, and that a skilled artisan would have a reasonable expectation of success (Office Action, pp. 5-6). The Office's conclusions regarding the cited references are based on speculations, and thus, the Office has not established a *prima facie* case of obviousness against claims 1, 7-21, and 29-33. Accordingly, Applicants respectfully traverse this rejection.

The Combination of WO 01/74164, Kishimoto, and Zhu Fails to Yield the Invention of Present Claims 1, 7-21, and 29-33

The Office combines WO 01/74164, Kishimoto, and Zhu stating that "it would have been obvious to one of ordinary skill in the art to cultivate hair inductive cells such as dermal papilla (DP) cells in a...medium [conditioned by prostate epithelial cells]" (Office Action, p. 5). The Office arrives at this conclusion by unjustifiably combining WO 01/74164 and Kishimoto, which disclose that Wnt signaling maintains the hair inducing activity of dermal papilla cells (see, e.g., p. 1183 of Kishimoto), with Zhu, which states that prostate cancer cells express multiple Wnt polypeptides (Abstract). None of WO 01/74164, Kishimoto, and Zhu, either singly or in combination, teaches or suggests a method for cultivating hair inductive cells, such as dermal papilla (DP) cells and dermal sheath (DS) cells, by culturing these cells in a medium that includes a prostate epithelial cell-conditioned medium, as is required by present independent claim 1, and claims dependent therefrom. WO 01/74164 and Kishimoto[1] merely state that Wnt3a and Wnt7a, and to some extent Wnt4, when recombinantly expressed in feeder cells (i.e., chick embryo fibroblasts), exhibit the ability to promote hair inducing activity in dermal papilla cells. Nowhere does WO 01/74164 or Kishimoto teach or suggest culturing dermal papilla or dermal

[1] The inventors of WO 01/74164 are also the authors of Kishimoto.

sheath cells in a culture medium conditioned by prostate epithelial cells, as is acknowledged by the Office ("While they do not teach prostate epithelial cells specifically"; Office Action, p. 5). Zhu fails to remedy this deficiency.

Zhu, which characterizes Wnt gene expression in prostate cancer cells and cultured primary prostate cells, fails to teach or suggest the use of these cells to produce a conditioned medium, much less that dermal papilla or dermal sheath cells, if cultured in such a conditioned medium, would retain hair-inducing activity. Furthermore, Zhu discloses that all of the prostate cells tested, including non-cancerous, primary cultured prostate epithelial cells (PrEC), lack expression of Wnt3a (see Figure 1, lane 1), which, along with Wnt7a, is one of the two Wnts disclosed by WO 01/74164 and Kishimoto that "showed a dramatic increase in hair growth" (see, e.g., page 26, lines 16-29). Additionally, not all of the prostate cells tested in Zhu showed expression of Wnt7a (see Figure 1, lane 1). Thus, the Office's conclusion that "given what is known in the art of prostate epithelial cells Wnt expression and it's ability to promote and maintain hair growth and inductivity, it would have been obvious at the time of the invention to culture DP cells in a medium conditioned with prostate epithelial cells" (Office Action, pp. 5-6) is simply a bald assertion without support.

The Office has failed to provide any "objective teaching in the prior art or...knowledge generally available to one of ordinary skill in the art [that] would lead that individual to combine the relevant teachings of the [cited] references" to achieve the invention of present claims 1, 7-21, and 29-33, as is required (*see, e.g., In re Fine*, 837 F.2d 1071, 1074, 5 USPQ.2d (BNA) 1596 (Fed. Cir. 1988)). Moreover, it appears that the Office has simply reconstructed the invention of

present claims 1, 7-21, and 29-33 using the present claims as the blueprint, which is impermissible hindsight reconstruction (see *Interconnect Planning Corporation v. Feil*, 774 F.2d 1132, 1139 and 1141, 227 USPQ (BNA) 543 (Fed. Cir. 1985); "It is impermissible to first ascertain factually what appellants *did* and then view the prior art in such a manner as to select from the random facts of that art only those which may be modified and then utilized to reconstruct appellants' invention from such prior art").

WO 01/74164 and Kishimoto fail to teach or suggest that medium conditioned by any cell that expresses a Wnt polypeptide, when used to culture dermal papilla cells, will suffice to promote or maintain hair-inducing activity; WO 01/74164 and Kishimoto simply do not teach or suggest that medium conditioned by prostate epithelial cells will suffice. The Office simply arrives at this conclusion by improperly combining the disclosures of WO 01/74164, Kishimoto, and Zhu, and extrapolating from those disclosures, without evidentiary support, the conclusion that because prostate epithelial cells express Wnts they are capable of producing a conditioned medium that will promote or maintain hair-inducing activity when used to culture dermal papilla or dermal sheath cells. This conclusion is erroneous.

WO 01/74164 and Kishimoto Fail to Teach or Suggest that All Cells Expressing Wnts are Capable of Maintaining the Hair Inductive Activity of Hair Inductive Cells

Neither WO 01/74164 nor Kishimoto teaches or suggests that any and all cell types expressing Wnt polypeptides, much less that all epithelial cells no matter the source, are capable of promoting the hair growth activity of hair inductive cells. Although WO 01/74164 teaches

that "DP cell[s] can be co-cultured with a cell which expresses Wnt" (p. 16, lines 18-20), WO 01/74164 fails to teach or suggest any non-recombinantly produced cells actually capable of achieving this result in co-culture with hair inductive cells. In fact, the only instance in which WO 01/74164 mentions specific cell types is in connection with genetic manipulation "to introduce[e] a nucleotide sequence encoding a Wnt polypeptide...into a particular cell, e.g., an epidermal cell or a DP cell", and the introduction of a cell into a subject (see, e.g., p. 16, lines 24-26, and p. 17, lines 10-17), neither method of which is relevant to present claims 1, 7-21, and 29-33. Even if WO 01/17464 or Kishimoto did describe the co-culture of hair inductive cells, such as DP cells, with non-recombinant epithelial cells or medium conditioned by such cells, which it does not, one of skill in the art would not consider prostate epithelial cells as a likely source. WO 01/74164 clearly states that "[t]he present invention is based, in part, on the discovery that Wnt proteins expressed in the follicular epithelium maintain anagen phase gene expression in dermal papilla cells and that hair inductive activity is also maintained by Wnt signaling" (WO 01/74164, p. 21, lines 5-7). Thus, one of skill in the art would be directed to cells of the follicular epithelium, not cells of the prostate epithelium.

Moreover, one of skill in the art, based solely on Zhu's description of the expression of multiple Wnt polypeptides in prostate epithelial cells, would have no reason to conclude, much less any reason to expect, that a conditioned medium from these cells would successfully promote or maintain hair inducing capability in dermal papilla or dermal sheath cells. A person of skill in the art might believe it is equally possible that prostate epithelial cells, which are present in a completely different tissue environment from that of the follicular epithelium that

includes hair inductive cells, express, in addition to Wnts, polypeptides that would inhibit or reduce hair inductive activity by dermal papilla and dermal sheath cells. Nothing in any of WO 01/17464, Kishimoto, or Zhu suggests otherwise. Thus, based on a proper reading and understanding of the cited publications, without hindsight, one of ordinary skill in the art would have no motivation to use prostate epithelial cells, which are of non-epidermal origin and present in a tissue that is not involved in hair production, to produce conditioned medium for culturing hair inductive cells, much less any reasonable expectation that prostate epithelial cells would be capable of producing conditioned medium capable of promoting or maintaining the hair-inducing activity of hair inductive cells during culture. Only the present inventors have demonstrated such activity using prostate epithelial cell-conditioned medium.

None of WO 01/17464, Kishimoto, or Zhu Provide Any Reason to Expect that Medium Conditioned by Prostate Epithelial Cells would Successfully Maintain Hair Inductive Activity of Hair Inductive Cells during Culture

For the present invention to be deemed obvious, there must be in the prior art something to suggest the invention, i.e., it must be obvious to try and there must be a reasonable likelihood of success. Neither condition is satisfied in the present case. The cited publications contain nothing that provides a reasonable likelihood of success, as is required for a finding of obviousness. This legal standard was set out by the Federal Circuit in *In re O'Farrell* (853 F.2d 894 (Fed. Cir. 1988); 7 U.S.P.Q.2d (BNA) 1673). More recently, the *O'Farrell* standard was reapplied by the United States Supreme Court in *KSR International Co. v. Teleflex Inc.* (127 S. Ct. 1727, 1739–40 (2006); 82 U.S.P.Q.2d (BNA) 1385; emphasis added), which held that a

combination that is obvious to try might be obvious under § 103 where there are "a finite number of identified, *predictable* solutions" and where "a person of ordinary skill has good reason to pursue the *known options* within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense." None of the predictable solutions provided by WO 01/74164 and Kishimoto involves the preparation of a medium conditioned by prostate epithelial cells and the use of that medium to culture hair inductive cells, nor do these publications, to the extent that they do describe media for use in culturing dermal papilla cells, provide any reason to use prostate epithelial cells as an alternative for producing a conditioned medium. Thus, neither of these publications, either singly or in combination, provides one of skill in the art with any reason to look beyond the follicular epithelium to identify cells that might be capable of producing a conditioned medium for use in maintaining the hair inductive activity of hair inductive cells during culturing, much less to prostate epithelial cells which lack expression of Wnt3a (see Fig. 1A of Zhu), which both WO 01/74164 and Kishimoto indicate exhibits the greatest capacity for maintaining hair inducing activity (see, e.g., Fig. 3b of Kishimoto, p. 1182). Moreover, even if there were a reason to combine the disclosures of WO 01/74164, Kishimoto, and Zhu, which Applicants do not concede, one of skill in the art would have no reasonable expectation based on this combination that prostate epithelial cells could be used successfully to produce a conditioned medium for culturing hair inductive cells. For all of these reasons, the Office has failed to establish a *prima facie* case of obviousness against present claims 1, 7-21, and 29-33.

The rejection of claims 1, 7-21, and 29-33 under 35 U.S.C. § 103(a) over the combination

of WO 99/01034, WO 00/69449, WO 01/74164, Kishimoto, and Zhu should be withdrawn.

CONCLUSION

In view of the above remarks, Applicants respectfully submit that the present claims are in condition for allowance, and such action is respectfully requested.

Enclosed is a petition to extend the period for replying for one month, to and including July 5, 2008.

If there are any additional charges, or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

Todd Armstrong, Ph.D.
Reg. No. 54,590

Date: 2 July 2008

for Paul T. Clark
Reg. No. 30,162

Clark & Elbing LLP
101 Federal Street
Boston, MA 02110
Telephone: 617-428-0200
Facsimile: 617-428-7045